EPO
Epidemiology Program Office
Issue 7

ADS Newsletter
Office of the Associate Director for Science
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Human Subjects Protection Abroad

What do you need to do when you are considering conducting research on human subjects in a foreign country?

The Code of Federal Regulation, Title 45, Part 46: Protection of Human Subjects – aka the *Common Rule* (http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm) - recognizes that procedures in foreign countries to protect human subjects in research may differ from those set forth in the regulation. Research may be approved, however, if "the procedures prescribed by the foreign institution afford protections that are at least equivalent to those provided in this policy" (45CFR46.101h). "Equivalent" refers to procedures as described in one of the internationally recognized ethical principles, i.e, *Declaration of Helsinki*, *Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects*, *CIOMS International Guidelines for Ethical Review of Epidemiologic Studies*, the *Belmont Report* or other internationally recognized principles approved by the Office for Human Research Protections (OHRP).

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Types of IRB Review

A review by the CDC Institutional Review Board (IRB) can be handled by a full IRB board or by expedited review depending on the nature of the research.

Full Board Review
The investigator should allow a minimum of 7-10 weeks from the time a completed protocol is received by the CDC Human Subjects Activity (HSA) for IRB full board review and decision. Delays longer than this are generally due to incomplete submissions. Most protocols submitted to the IRB undergo at least one round of revisions.

Expedited IRB Review
Under an expedited review procedure, the review is carried out by the IRB Chair or the Chair's designee, without waiting for a scheduled meeting. The EPO Office of the Associate Director for Science (OADS) makes the initial determination of whether a new protocol, amendment, or continuation request is eligible for expedited review. Research activities may be eligible for expedited review if all of the following criteria are met:

1. the research activities present no more than minimal risk to human subjects;
2. the data collected in the research are non-identifiable;
3. the research involves well accepted and usual procedures (e.g., collection of blood samples by finger stick, heel stick, ear stick, or venipuncture).

Continuation of Protocol Approvals
Initial IRB approvals are in effect for 1 year or until the study is completed (whichever occurs first). The investigator is responsible for the timely submission of a continuing review application to the IRB that previously reviewed the protocol. To assist investigators in submitting

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Ethical Dilemmas in Public Health

Scenario 1: There is an American doctor in the village!

In foreign countries, especially in developing countries, a doctor from the United States is almost always looked upon as an expert. It is not uncommon to see patients being brought for consultation and expert advice when words get around that "there is an American doctor in the village."

Without a license to practice medicine in a country of temporary duty, what are the ethical/legal issues that could arise should there be an emergency and the only doctor in sight is the EIS officer?

As a doctor, the officer has a moral and ethical obligation to help. However moral/ethical obligation doesn't necessarily translate to legal protections. The officer's action may incur liabilities if something goes wrong. Although the officer has no legal obligation to help, many, if not most, will likely place themselves at risk to offer needed assistance. The officer generally must make his or her own decision regarding providing treatment in these situations. However, several sources are available for guidance. Specific policies or agreements may have been made regarding the assignment, so the officer is encouraged to gain as much information as possible before heading off for the assignment. It is always a good idea to check with the collaborator(s) in the country beforehand on what the country's policies are for foreign doctors. It is also helpful to learn about the local customs, which can provide clues as to how people will react if something went wrong while administering aid. People may be grateful no matter what the outcome is. On the

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Special or Vulnerable Populations

Selecting special or vulnerable populations as research subjects requires additional procedures to protect them given their natural vulnerability. The *Common Rule* describes additional protections for certain populations in addition to the protections provided under subpart A. Additional protections are provided under subpart B to pregnant women, human fetuses and neonates, subpart C to prisoners, and subpart D to children. Other vulnerable populations including mentally disabled persons, and economically or educationally disadvantaged individuals are not described in the *Common Rule*; however, these and other similar populations should also be given special considerations.

Pregnant women, human fetuses and Neonates (45CFR46 Subpart B)

Pregnant women, human fetuses and neonates may be involved in research only if certain conditions are met including:

1. Any risk is the least possible for achieving the objectives of the research;
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
3. If the research holds out the prospect of direct benefit to the pregnant woman or to both the pregnant woman and the fetus or no prospect of benefit to both when risk to the fetus is no greater than minimal, the informed consent from the mother be sought;
4. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father be sought, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest;
5. For children who are pregnant, assent and permission be obtained in according to 45CFR46, Subpart D of the *Common Rule;*
6. No inducements will be offered to terminate pregnancy;
7. Researchers shall have no part in any decisions in the timing, method, or procedure used to terminate pregnancy;
8. Research shall have no part in determining the viability of a neonate.

Prisoners (45CFR46 Subpart C)

A prisoner is defined as any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trials, or sentencing.

The IRB can approve such research only if it meets the following requirements (45 CFR 46.305 and 45 CFR 46.306):

1. The research under review represents one of the following categories:

(a) Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the participants.

(b) Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the participants.

(c) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction and sexual assaults). Following approval by the CDC IRB, the Deputy ADS will notify OHRP who will provide, via Secretary's (of DHHS) panel, final approval for the research.

(d) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the participant. In cases in which those studies require the assignment of prisoners to control groups which may not benefit from the research, upon approval by the CDC IRB, the Deputy ADS will notify OHRP who will provide, via Secretary's (of DHHS) panel, final approval for the research.

2. Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired.
3. The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers.
4. Procedures for the selection of participants within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the investigator provides to the IRB justification in writing for following some other procedures, control participants must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project.
5. The information is presented in language that is understandable to the participant population.
6. Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and that each prisoner is clearly

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informed in advance that participation in the research will have no effect on his or her parole.

7. Where the IRB finds that there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

Upon approval of the protocol by the IRB, the CDC Deputy ADS will notify OHRP about the research, the category under which it is permitted (45 CFR 46.306) and that the duties of the IRB under 45 CFR 46.305 have been fulfilled.

Note: Effective June 20, 2003 the Secretary of Health and Human Services (DHHS), pursuant to 45 CFR 46.101(i), has waived the applicability of certain provisions of subpart C of 45 CFR part 46 (Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects) to specific types of epidemiological research involving prisoners as subjects (See Update on page 5).

Children

Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted (46.402(a)). This definition, when read in the context of the Federal Regulations requires a review of state or local law to determine the age at which an individual can consent to participation in research without parental permission. An important aspect of IRBs' considerations of research involving children is an evaluation of what constitutes "minimal risk." Procedures which generally present no more than minimal risk to healthy children include urinalyses, small amounts of blood obtained by venipuncture, electroencephalography (EEG), allergy scratch tests, minor changes in diet or daily routine, and/or the use of standard psychological or educational tests. However, the assessment of the probability and magnitude of harm or discomfort may be different in ill children and may vary depending on the diseases or conditions that the children may have. For example, obtaining research blood samples from a very ill and anemic child may present more than minimal risk to the child. The IRB must also consider the extent to which research procedures would be a burden to a child-participant, regardless of whether the child is accustomed to the proposed procedures. Procedures that exceed minimal risk may be difficult to define in the abstract, but should not be difficult to identify on a case-by-case basis. Higher-risk procedures might include biopsy of internal organs, spinal taps, or the use of drugs whose risks to children have not yet been established. Behavioral interventions likely to cause psychological stress also may exceed minimal risk.

The IRB shall approve research involving children only if the following conditions are met:

1. Research not involving greater than minimal risk that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects
   (a) The risk is justified by the anticipated benefit to the subjects;
   (b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
   (c) Adequate provisions are made for soliciting the assent of the children and permission of the parents or guardians.
3. Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition
   (a) The risk represents a minor increase over minimal risk;
   (b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
   (c) The intervention or procedures is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
   (d) Adequate provisions are made for soliciting assent of children and permission of their parents or guardians.
4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health of welfare of children
   (a) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
   (b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:
      1) That the research in fact satisfies the conditions of 46.404, 46.405, 46.406 or
      2) The following:
         i. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
         ii. The research will be conducted in accordance with sound ethical principles;
         iii. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.

Assent of the Children (45CFR46.408)

When children are involved in research, the IRB must make provisions for the assent of the children and the permission of the parents. The IRB must determine

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1. Scientific Ethics Training
All investigators who wish to become involved in human subjects research must take the CDC Scientific Ethics Training and obtain a scientific ethics verification number (ethics number). The ethics number must accompany the research protocol when it is submitted for review. More information on the Scientific Ethics Training can be found on the EPO ADS Website at http://www.cdc.gov/epo/ads/newsletters/adsnews-6-ethicstraining.htm.

2. Assurance
If investigators from foreign institution(s) are collaborating on the research project, the institution(s) must have assurance filed with OHRP. An assurance is a document that OHRP requires both CDC and other involved institution(s) to sign showing each institution's commitment to the ethical principles governing research with human beings. Signatures are required from the host country's ethics committee chairperson and an official from the collaborating institution who can bind the institution to the tenets of the ethical principles as described in one of the internationally accepted guidelines mentioned above. For more information about assurance, contact Virginia Talley, CDC Assurance Coordinator, at 404-498-3110 or vtalley@cdc.gov.

3. CDC Institutional Review Board and Host country's Ethics Committee Approvals
After 1 and 2 above have been accomplished, the Principal Investigator of the research project must seek CDC Institutional Review Board (IRB) and the host country's ethics committee approvals. Both the IRB and the Ethic Committee in the host country where the research is to be conducted must approve the research. The country ethics committee designated under the Assurance, as mentioned above, must also register with OHRP. Information on how to apply for a FederalWide Assurance (FWA) and to register an IRB can be found at http://ohrp.osophs.dhhs.gov/irbasur.htm or contact CDC Assurance Coordinator at the contact information above.

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continuation requests in a timely fashion, 60 and 30 days before protocol expiration, the CDC HSA notifies the investigator of the upcoming deadline via registered e-mail.

The investigator is asked to submit a *Request for Approval of Continuation of Protocol Approval*, CDC form 0.1251, along with the currently approved informed consent document if participants are being accrued, 45 days before the expiration date.

If changes in the protocol are substantive or there are changes in the consent document, data collection instruments, or site locations, an amendment request (CDC form 0.1252) should be submitted along with the continuation request.

If the continuation request is not received by the protocol's expiration date, the IRB will terminate the approval of the protocol.

Amendment
If changes to the protocol, consent form, or other study documents that differ from what was approved by the IRB, are made, the investigator must submit a description of and justification for the change in the protocol, along with CDC form 0.1252, *Request for Amendment,* to the IRB through the EPO OADS. An amendment should be submitted as soon as possible, before the implementation of the change. If it is a minor amendment that presents no additional risks to the participant (e.g., additional sites added, submission of site specific consent forms, revisions of data collection documents that do not add increased sensitivity to the originally approved protocol, expansion of the study population that does not include inclusion of new categories of participants, addition/deletion of laboratory tests that do not increase the risk or impact the validity of the study), the review and approval are handled by the expedited review process. Anything other than a minor amendment must go to the full IRB for approval. If significant findings are reported in the literature that may result in a change in the risks or benefits associated with the study or require a change in the protocol, the investigator should report the literature findings to the IRB immediately along with recommended corrective actions to the protocol for approval. Failure to submit an amendment when changes are made may result in a termination of the protocol and the investigator may need to resubmit the protocol for IRB review.

Closure
Completion of a study is defined as completion of data analysis or removal of identifying information from the data. Once the study is completed, a notice should be submitted to the HSA through the EPO OADS, using CDC form 0.1253, *Request for Closure of Human Subjects REsearch Protocol*. The same procedure should be used for studies that were cancelled (never started) after submission to the HSA. The EPO supervisor should be consulted about studies that continue after the investigator leaves CDC.

Deferral (See article on Deferral of IRB Review on page 6).

Useful Websites and Links

Office for Human Research Protections
http://ohrp.osophs.dhhs.gov/index.html

Office of Research Integrity
http://www.ori.dhhs.gov/

EPO Associate Director for Science
http://www.cdc.gov/epo/ads/index.htm

EPO Overview of Scientific Procedures
http://www.cdc.gov/epo/ads/contents.htm

EPO ADS Newsletter Back Issues
http://www.cdc.gov/epo/ads/newsletters/adsnews.htm

CDC Associate Director for Science
http://www.cdc.gov/od/ads/index.htm

CDC Privacy Rule
http://www.cdc.gov/privacyrule

CDC IRB Forms
http://www.cdc.gov/od/ads/hsrirb.htm

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whether the permission of both parents is required.

Although children are not capable of giving legally valid consent, they may be able to assent or dissent from participation. Out of respect for children as developing persons, they should be asked whether they wish to participate in research, particularly if they can comprehend and appreciate what it means to be a volunteer for the benefit of others and that research is not likely to benefit them directly. Taking into account such factors as the nature of the research, and the age, status and medical condition of potential participants, the IRB must determine for each protocol whether all or some of the children are capable of assenting to participation. There is no requirement that assent be sought at a specific age, but that it be sought when in the judgment of the IRB, the children are capable of providing assent. Generally, CDC IRBs require that assent be obtained from children 7 years of age and older.

Wards of the State (45CFR46.409)

Children who are wards of the state or any other agency, institution, or entity can be included in research only if such research is: (1) related to their status as wards; or (2) conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as participants are not wards.

The IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

OHRP Update: Secretarial Waiver for Epidemiological Research Involving Prisoners

(June 20th, 2003) The Secretary of Health and Human Services (DHHS), pursuant to 45 CFR 46.101(i), has waived the applicability of certain provisions of subpart C of 45 CFR part 46 (Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects) to specific types of epidemiological research involving prisoners as subjects. This waiver, effective June 20, 2003, will allow DHHS to conduct or support certain important and necessary epidemiological research that would not otherwise be permitted under subpart C.

The Secretary of HHS has waived the applicability of 45 CFR 46.305(a)(1) and 46.306(a)(2) for certain epidemiologic research conducted or supported by DHHS

(1) in which the sole purposes are:

(i) to describe the prevalence or incidence of a disease by identifying all cases, or

(ii) to study potential risk factor associations for a disease, and

(2) where the institution responsible for the conduct of the research certifies to the Office for Human Research Protections, acting on behalf of the Secretary, that: the institutional review board (IRB) approved the research and fulfilled its duties under 45 CFR 46.305(a)(2)-(7) and determined and documented that

i. the research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and

ii. prisoners are not a particular focus of the research,

The waiver can be accessed as a pdf document at http://ohrp.osophs.dhhs.gov/references/fr06-20.pdf. For further information, contact the OHRP Prisoner Research Contact Person at (301) 496-7005 (phone) or (301) 402-0527(fax).

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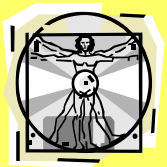
other hand, people may feel resentful if the officer refuses to help, which could ultimately have a negative impact on the overall success of the public health mission and jeopardize future work in the particularly community. Ultimately, the decision to intervene rests on the officer, who is usually aware and accepts the potential personal risk.

Scenario 2: Why would we put a lot of work and resources to establishing an ethics committee so you could put your name on a paper?

A CDC investigator is assigned as a consultant in a developing country. Recognizing the public health benefits of an ethics committee, the investigator wants to recommend to the Ministry of Health (MOH) that such a committee be established. However, the MOH appears unwilling to invest the resources to form a committee. What should the investigator tell the MOH staff to persuade them to establish an ethic committee?

Most likely, the MOH already has an idea of what the public health benefits would be, but the investigator would do well to reiterate these benefits, e.g., improve research practices, better cooperation between investigators and research subjects, improved international cooperation. These benefits should be described in detail, as well as any additional long-term benefits, what the processes and requirements are for forming a committee, and the kind of resources needed. The MOH may find that it is more feasible than they thought. It may help to provide specific examples of the benefits and experiences from other countries. An additional consideration for the MOH is that, from CDC perspective,the investigator is limited as to the types of activities he or she can be involved in, particularly research involving human subjects. Some of these restrictions may be overcome if the research can be reviewed and approved by a local ethics committee and the CDC IRB.



CDC Policy on Deferral of IRB Review

The CDC Deputy Associate Director for Science makes determinations regarding all deferrals. Investigators should not be involved in any research/contact with human subjects until a determination regarding deferral status has been made.

- **Reliance on the CDC IRB by an Outside Institution**

CDC will accept the request of an outside institution to defer review of a protocol to the CDC IRB. Reliance on the CDC IRB is subject to the following two limitations. First, CDC must be engaged in the research and the protocol must be scheduled for review or have been reviewed by the CDC IRB. Requests for deferral when the CDC IRB is not otherwise required to review the protocol will not be accepted. Second, the requirement of the Office of Human Research Protections (OHRP) for knowledge of the local research context must be addressed either in review by a third institution engaged in the research or by the addition of expertise in this area to the CDC IRB. Inability to address this concern might result in the decision not to accept the request to defer to the CDC IRB.

To facilitate this process, a state or local health department or other research partner should consider designating the CDC IRBs on either the initial or an update application for a Federalwide Assurance (FWA). Specific information on how to complete the FWA form is available from the CDC Assurance Coordinator, Virginia Talley at 404-639-4026.

- **CDC Reliance on Another Institution's IRB for a Study that has not been Initiated**

CDC is willing to consider relying on another IRB covered by an OHRP assurance (multiple project assurance or FWA) based on the following criteria:

1. The study involves no more than minimal risk and does not address a controversial topic.
2. CDC did not originate nor control development of the protocol.
3. CDC investigators do not have any direct interaction with study participants.

Four other considerations in the process are also reviewed:

1. The study does not involve vulnerable populations. However, certain studies involving children and adolescents that meet the other criteria above can be eligible for consideration for deferral and will be reviewed individually to ascertain the degree of risk and inclusion of appropriate parental permission and child assent procedures. Studies involving prisoners or targeting pregnant women, human fetuses or neonates will not be eligible for deferral.
2. CDC investigators do not have access to individually identified data from the study.
3. CDC investigators do not retain/store specimens for future research.
4. The study has not begun (except as outlined below).

- **Retrospective Review of Research Study Already Under way**

CDC may consider deferring review to an outside IRB when CDC investigators are invited to participate in a research project that has already been initiated. CDC investigators may not participate in any project not approved by CDC.

The following must be met before CDC will consider deferring this type of request:

1. The institution to which CDC defers must hold an OHRP assurance, and the IRB must be in a position to be responsible for review of the conduct of the study at all participating sites.
2. Ongoing monitoring of the study from the lead IRB will be required, and documentation of approval of amendments, review of adverse events and continuation review must be submitted to the CDC HSA on a periodic basis not to exceed yearly on the date of annual review.
3. All other conditions for reliance on another IRB must be met. No amendment or alteration of the protocol may be implemented without prior approval by the CDC HSA, which would substantially affect these conditions as outline in the preceding paragraphs (e.g., inclusion of activities which alter the minimal risk determination, inclusion of prisoners, or targeting of pregnant women). Violation of these conditions may result in termination of CDC participation in the project.
4. The investigator must provide clear and reasonable justification as to why the protocol was not submitted for CDC review prior to the initiation of contact with human subjects.

When the project is not submitted in the correct time frame, e.g., when CDC investigator was involved in the project before submission of the request to IRB, the protocol will be reviewed by the full CDC IRB board.

For deferral submit *Request for Deferral of New Protocol to another Institutional IRB,* CDC form 0.1256 along with the complete protocol to your supervisor.

EPO ADS Newsletter

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EPO ADS Staff Update

The ADS Office would like to welcome **Robin Ikeda** who serves as the new EPO ADS and **Anissa Ham**, who serves as the Project Officer for the Urban Research Center. You can reach Robin and Anissa at 404-639-3683. We would also like to thank Ronald Moolenaar for serving as Acting ADS during the month of May.